MS/04/43157

THE PATENTS ACT, 1970

It is hereby certified that annexed hereto is a true copy of Application & Provisional Specification filed in respect of Patent Application No. 1049/CHE/2003, dated 23/12/2003 by Dr. Reddy's Laboratories Limited, an Indian company having its registered office at 7-1-27, Ameerpet, Hyderabad-500 016, Andhra Pradesh, INDIA.

.....

.....**In witness thereof**

I have hereunto set my hand

Dated this the19th January, 2005
29th day Pausa, 1926 (Saka)

M. S. V

(M.S. VENKATARAMAN)
ASSISTANT CONTROLLER OF PATENTS & DESIGNS

PA NT OFFICE BRANCH
GO RNMENT OF INDIA
Gu omplex, 6th Floor, Annex.II
No. Anna Salai, Teynampet, Chennai – 600 018.

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)
APPLICATION FOR GRANT OF A PATENT
(Section 5(2), 7, 54 and 135 and Rule 33A)

1. I/We, Dr. Reddy's Laboratories Limited, an Indian company having its registered office at 7-1-27, Ameerpet, Hyderabad, Andhra Pradesh, INDIA, 500 016
2. hereby declare -
   (a) that I am/ we are in possession of an invention titled **"Novel crystalline forms of Ezetimibe and process for preparation thereof"**
   (b) that the provisional specification relating to this invention is filed with this application.
   (c) that there is no lawful ground of objection to the grant of a patent to us.
3. further declare that the inventor(s) for the said invention is/are **Sundaram Venakatraman, Srinivasan Thirumalai Rajan, V.Pattabhi Ramayya, S.Vishnu vardhan, B. Subrahmanyam, Ch.V.A.Sasikala,** All citizens & residents of India belonging to **Dr. Reddy's Laboratories Limited, 7-1-27, Ameerpet, Hyderabad – 500 016, Andhra Pradesh.**
4. We claim the priority from the application(s) filed in convention countries, particulars of which are as follows.
5. We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which I/We are the applicant/patantee
6. We state that the application is divided out of my/our application, the particulars of which are given below and pray that this application deemed to have been filed on _____ under section 16 of the Act.
7. That We are the assignee or legal representative of the true and first inventors.
8. That my/our address for service in India is as follows:

Sundaram Venkataraman,
Vice president R&D
Dr. Reddy's Laboratories Limited
7-1-27, Ameerpet
Hyderabad, A.P., 500 016
Phone: 040- 3095578
Fax: 040-3095438

104/CHE/2003
23-12-2003

9. Following declaration was given by the inventor(s) or applicant(s) in the convention country:
We, the true and first inventors for this invention or the applicant(s) in the convention country declare that the applicant(s) herein is/are my/our assignee or legal representative

(Signed) S. Venkataraman

Sundaram Venkataraman,
Plot No.141,
Flat No.202,
Sharada Nilayam,
Moti Nagar,
Hyderabad-500018

(Signed)

Srinivasan Thirumalai Rajan,
Plot No. 12,
Lake view Enclave,
Miyapur,
Hyderabad-500 050.
Andhra pradesh,
India.

Signed) V. Pattabhi Rama

Vaddadi Pattabhi Ramayya
H.No: 24-138/4,
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Malkajgiri,
Hyderabad-500047.
Andhra pradesh,
India.

(Signed)

Sunkara Vishnu vardhan,
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Andhra pradesh, India.

Signed) B. Subrahmanyam.

Bulusu Subrahmanyam,
D. No: 7-148,
Venkataraju nagar,
China amiram
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W. Godavari District- 534204
Andhrapradesh
India.

(Signed) Ch. V. A. Sasikala.

Cheemalapati venkata annapurna sasikala;
D/o. Ch. Koteswara rao
D. No: 38-31-102.
Green gardens,
Marripalem
Visakhapatnam,
Pin: 530018

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to me/us on this application.

11. Following are the attachments with the application
(a) Provisional specification (---4--- pages, in triplicate)
(b) Drawings (------- pages, in triplicate)
(c) Priority documents(s)
(d) Statement and Undertaking on Form-3.
(e) Power of authority
(f) Abstract of the invention (------- page, in triplicate)
(g) Fee Rs.3000.00 (three thousand rupees only) in cheque bearing No. 266780 dated 28.11.2003 drawn on HDFC Bank Limited, Lakdi-kapul, Hyderabad– 4.

I/We request that a patent may be granted to me/us for the said invention.

Dated this 10th day of December 2003.

(Signed) S. Venkataraman
Sundaram Venkataraman,
Vice President (R&D)
Dr. Reddy's Laboratories Limited.

To,
The Controller of Patents
The Patents Office Branch, Chennai.

FORM 2

THE PATENTS ACT, 1970

PROVISIONAL SPECIFICATION

(SECTION 10)

1049/CHE/2003
23-12-2003

Novel Crystalline forms of Ezetimibe and Process for preparation thereof.

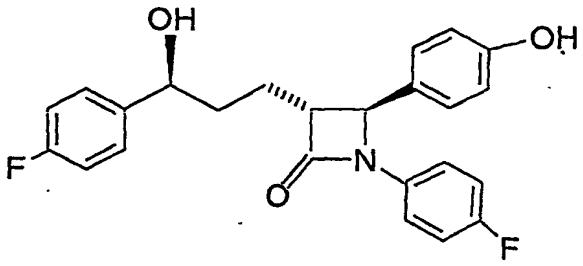
Dr. Reddy's Laboratories Ltd.
an Indian Company having its registered office at
7-1-27, Ameerpet
Hyderabad – 500 016, A.P., India

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

Field of the Invention:

The present invention related to novel crystalline forms of (3R, 4S)-1-(-4-Fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-2-azetidinone, which is generically known as Ezetimibe and process for the preparation there of,

Ezetimibe can be shown as Formula (I)



Formula (I)

Ezetimibe is useful as hypocholesterolemic agents in the treatment of prevention of ather--osclerosis.

Background of the invention:

USP 5,767, 115 which is a basic patent of Ezetimibe discloses the process for the preparation of Ezetimibe and the said patent specifically claims Ezetimibe.

USP 6,207,822 and USP 5,856,473 both the patents discloses the process for the preparation of Ezetimibe. The '822 patent discloses the process which comprises reaction of 3-{2-[3-(fluorophenyl)-3- (trimethyl silyloxy)-propyl]-3-(4-fluoro phenyl amino)-3-(4-trimethyl silyloxy phenyl)-1-oxo-propyl}-4-(S)-phenyl oxazolidin-2-one with bistrimethyl silyl acetamide and t-butyl ammonium fluoride in t-butyl methyl ether followed by quenching with acetic acid then followed by reaction with sulfuric acid in isopropyl alcohol solvent. The obtained crude material is crystallized from aqueous isopropyl alcohol. Ezetimibe obtained by this process is in crystalline nature.

The '473 patent discloses a process for the preparation of Ezetimibe, which comprises the reduction of 1-(4-fluorophenyl)-3(R)-(3-(4-fluorophenyl)-3-hydroxypropyl)-4(S)-(4-benzyloxyphenyl)-2-azetidinone in the presence of Pd/C in ethanol under the pressure of H_2 gas. The said patent does not disclose the physical character of Ezetimibe obtained by this process.

Polymorphism can be defined as the ability of the same chemical substance to exist in different crystalline structures. The different structures are referred to as polymorphs, polymorphic modification or form.

Hence, the first object of the present invention is to provide the novel crystalline forms of Ezetimibe.

The second object of the present invention is the process for the preparation of the novel crystalline forms of Ezetimibe.

Here in after for the of convenience crystalline forms are referred as form-I and form-II

The novel crystalline forms of Ezetimibe of the present invention is well suited for *pharmaceutical formulations and can be used in the treatment of atherosclerosis diseases.*

Summary of the Invention:

The present invention is directed to provide a novel crystalline forms of Ezetimibe.

The present invention also embodies a process for the preparation of a novel crystalline forms of Ezetimibe, which comprises, 3-{2-[3-(fluorophenyl)-3- (trimethyl silyloxy)-propyl]-3-(4-fluoro phenyl amino)-3-(4-trimethyl silyloxy phenyl)-1-oxo-propyl}-4-(S)-phenyl oxazolidin-2-one with bistrimethyl silyl acetamide in tert. butyl methyl ether followed by quenching with organic acid then followed by reaction with protic acid in an alcoholic solvent. Filtered the compound and the wet compound dried at aerially for 10-40 hours.

The present invention further provides a process for the conversion of an Ezetimibe to a novel form. The process comprises Ezetimibe crystalline compound, making pellet by applying pressure then powdered the pellet.

Detailed description of the invention:

The present invention provides the novel crystalline forms (form-I and form-II) of Ezetimibe and process for its preparation.

The process for the preparation of novel crystalline form (from-I) of Ezetimibe comprises:

(i) reacting 3-{2-[3-(fluorophenyl)-3- (trimethyl silyloxy)-propyl]-3-(4-fluoro phenyl amino)-3-(4-trimethyl silyloxy phenyl)-1-oxo-propyl}-4-(S)-phenyl oxazolidin-2-one with bistrimethyl silyl acetamide in t-butyl methyl ether;

(ii) quenching the reaction solution of step (i) with acetic acid then followed by reaction with sulfuric acid in solvent such as isopropyl alcohol, ethanol or/and methanol;

(iii) filtration of the compound from step (ii) and the wet compound dried aerially for 10-40hrs, preferably for 20-24hrs;

MC of the obtained compound having the range of 3.0 to 5.0% w/w.

This invention also embodies for the preparation of novel crystalline form (form-II) of Ezetimibe can be prepared from the crystalline form of Ezetimibe, which comprises;

(i) making pellet of crystalline form of ezetimibe by applying pressure;

(ii) powdering the compound of step(i) by conventional methods;

(iii) drying the compound of step (ii) to get form-II.

MC of the obtained compound having the range of 0.5 to 3.0%w/w.

It is note worthy to mention that starting material crystalline form of Ezetimibe which is used in our invention can be prepared as per the process in USP 6,207,822.

Hence, the present invention is directed to provide novel crystalline forms (from-I and form-II) of Ezetimibe and process for the preparation thereof. The process for the preparation of crystalline forms (form-I and form-II) of Ezetimibe of the present invention is simple, eco-friendly and commercially viable.

Dated: 22nd day of December 2003.

Signed: S. Venkataraman

Sundaram venkataraman,
Vice-President (R&D),
Dr. Reddy's Laboratories Limited.

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/US04/043157

International filing date: 23 December 2004 (23.12.2004)

Document type: Certified copy of priority document

Document details: Country/Office: IN
Number: 1049/CHE/2003
Filing date: 23 December 2003 (23.12.2003)

Date of receipt at the International Bureau: 15 February 2005 (15.02.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse